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Review

Polarization and asymmetry in T cell metabolism

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ABSTRACT

T cell activation results in a rapidly proliferating T cell endowed with a metabolic phenotype necessary for growth and division. However, before the cell can proceed towards this burst of cell division a phase of quiescence occurs, during which the basic mechanisms governing regulation of metabolic reprograming are established. This review focuses on key cellular processes controlling early metabolic regulation and how these circuits of metabolic control dictate distinct cellular fates upon the first asymmetric division.

Contents

1. Introduction

When a lymphocyte is activated to proliferate, a lag phase of about 24 h is followed by a remarkable burst of cell division, completing a cell cycle every 6–8 h (and in the case of $CD8^+$ T cells, every 4–6 h) [1]. It follows, therefore, that lymphocytes "reprogram" themselves to meet the high metabolic demands of such proliferation. This review addresses this from the perspective of T lymphocytes, how this reprogramming occurs, and how, in turn, it transmits to the daughters of the dividing cell to determine cell fate.

Activation of T cells upon ligation of the TCR-CD3 complex by MHC-bound antigen on antigen presenting cells (APCs) results in Phospholipase C γ (PLCγ)-dependent generation of the secondary messengers inositol-3-phosphate (IP_3) and diacylglycerol (DAG). TCR-induced production of DAG activates Ras- and Protein Kinase C θ (PKCθ)- dependent signaling pathways, whereas IP_3 triggers increased intracellular Ca^{2+} levels. TCR signaling also increases intracellular levels of reactive oxygen species (ROS) [2]. Together, these signals activate the transcription factors Nuclear Factor of Activated T cells (NFAT), Activator Protein 1 (AP-1), and Nuclear Factor of Kappa light chain enhancer in B cells (NF-κB), all of which are essential to drive cytokine production, T cell proliferation, and differentiation [3].

TCR ligation also results in T cell polarization as the microtubule organizing center (MTOC) moves to the immunological synapse (IS) formed at the T cell-APC contact site [3]. The distal pole complex

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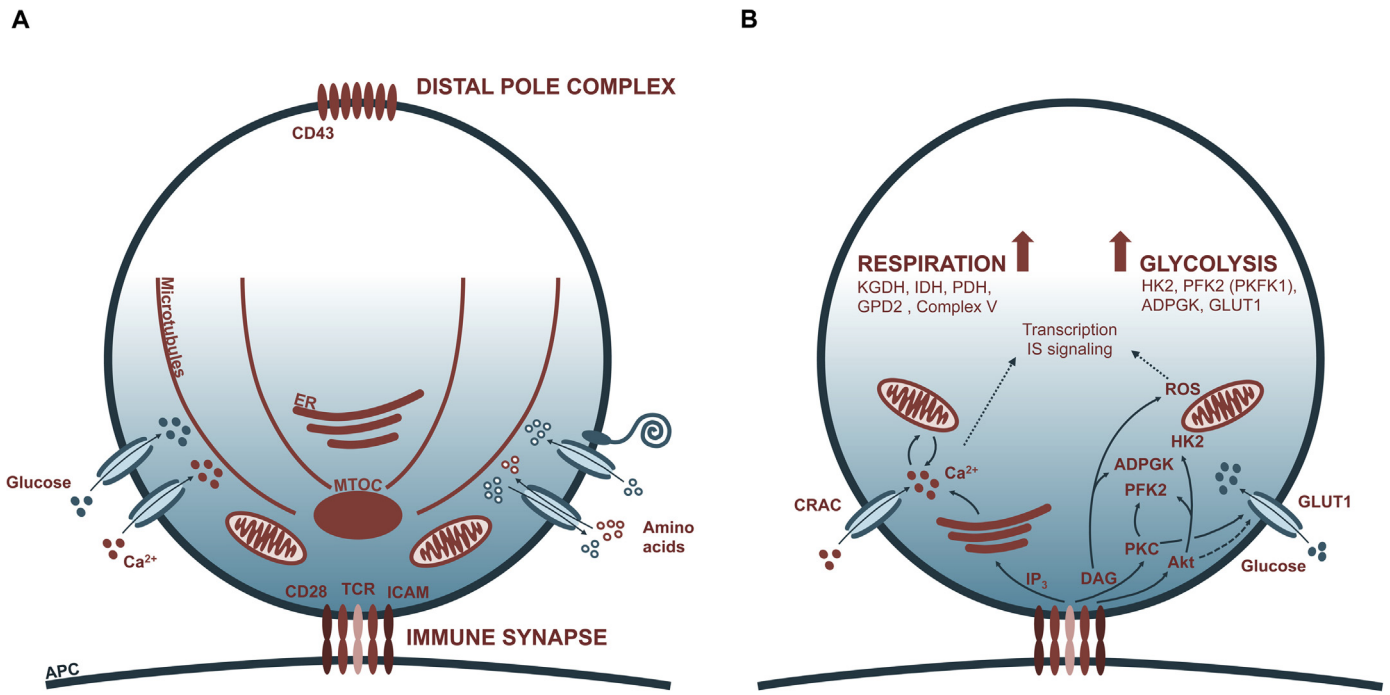

Fig. 1. T cell activation-induced polarization (A) and metabolic signaling (B).
A, Association of a T cell with an antigen-presenting cell (APC) via the immune synapse (IS shading: dark – ICAM-1/LFA-1, lighter – CD80 or CD86/CD28, light – peptide-MHC/TCR) induces relocation of the microtubule organizing center (MTOC) and mitochondria towards the IS. The distal pole complex forms at the opposite position. T cell activation induces an influx of Ca^{2+} (via CRAC channels), glucose (via GLUT1) and amino acids e.g., neutral amino acids, (glutamine, via the SLC1A5 (ASCT2) transporter); neutral branched (valine, leucine, isoleucine) and aromatic (tryptophan, tyrosine) amino acids (via CD98 (SLC3A2)/SLC7A5 heterodimeric complex). CRAC and CD98 are redistributed towards the IS. B, IS formation triggers IP_3-dependent Ca^{2+} release from ER, which in turn leads to influx of extracellular Ca^{2+} (via CRAC channels) regulated by mitochondrial Ca^{2+} buffering. Mitochondrial Ca^{2+} uptake contributes to an increase in respiration via activation of enzymes: KDH, IDH, PDH, GPD2 and Complex V (ATP synthase). Glycolysis is increased by TCR-generated DAG, and thus activation of GLUT-1, ADPGK and PFK2 as well as CD28-induced Akt triggering leading to PFK2 activation and recruitment of GLUT-1 to plasma membrane and HK2 to mitochondria. Mitochondrial ROS together with Ca^{2+} signal activate transcriptional response and modulate signaling at the IS.

(DPC) forms opposite the MTOC and IS, thereby creating an axis of asymmetry within the undivided cell. Within minutes, massive rearrangement of the cytoskeleton further manifests polarization by providing the infrastructure for directed transportation of cargo towards either of the two cell poles. By polarization of cellular sites that serve as metabolic hubs, such as plasma membrane, mitochondria, endoplasmic reticulum (ER), Golgi apparatus, and lysosomes, the cell facilitates polarization of metabolic events. Several of these events are summarized in Fig. 1 and are detailed below.

2. Metabolic hubs in T cell activation

2.1. Cytoplasm and plasma membrane

Upon activation, T cells switch their metabolism from oxidative phosphorylation to aerobic glycolysis to meet their high anabolic demands. Ras- and Erk-dependent induction of c-Myc transcription, translation, and stabilization, are essential to drive this metabolic reprogramming, which in some T cell subsets is further sustained by Akt- and Mammalian Target of Rapamycin Complex 1 (mTORC1)-mediated Hypoxia-Inducible Factor-1 (HIF1) stabilization [4–6]. In addition, a number of metabolic events independent of gene expression-driven reprograming are induced as immediate consequences of TCR and/or CD28 receptor triggering.

A rapid increase in glucose uptake and glycolytic flux (lactate release) occurs within minutes of TCR stimulation or treatment with phorbol myristate acetate (PMA; DAG mimetic) plus ionomycin (Ca^{2+} ionophore) of naïve or memory $CD8^+$ T cells in transient or sustained fashion, respectively [7–9]. The observation that phorbol esters alone up-regulate glucose transport by inducing phosphorylation of glucose transporters [10] suggests that the immediate-early switch to glucose metabolism could be mediated exclusively by TCR-induced DAG (PMA) signal without a need for additional CD28-mediated Akt stimulation. In line with this observation, it was recently demonstrated that GLUT-1, a major glucose transporter in T cells [11], is activated by PKC-mediated phosphorylation, which can be triggered with PMA [12]. The PKC isoform responsible for this regulatory mechanism remains to be identified. However, rapid, Akt-dependent transport of intracellular GLUT-1 towards the plasma membrane may augment this PKC-mediated activation [13]. PKC- and Akt-induced signaling may also converge at the level of activation of Phosphofructokinase 1 (PFK1), a rate-limiting enzyme in glycolysis [14]. Both PKC and Akt phosphorylate and activate Phosphofructokinase 2 (PFK2), thereby stimulating synthesis of fructose-2,6-bisphosphate, an allosteric activator of PFK1.

Phosphorylation of glucose, a first step of glycolysis, is yet another stage where DAG and Akt signaling can converge to enhance glycolytic flux upon T cell activation. Akt phosphorylates Hexokinase-2 (HK2) at Thr473, which results in mitochondrial association of HK2 and an increase in glycolytic flux by providing HK2 a preferential access to the ATP pool newly formed by mitochondria [15–17]. Meanwhile, the ER-associated alternative glycolytic enzyme, ADP-dependent Glucokinase (ADPGK), is transiently activated upon TCR stimulation in a DAG-dependent manner, using ADP to generate glucose-6-phosphate, and thus fueling glycolysis [9]. In contrast, however, it has been demonstrated that Phosphatidylinositol 3-kinase (PI(3)K) and Akt may not be required for TCR-mediated initiation of glucose uptake or glycolysis in naive $CD8^+$ T cells [18]. Further, in response to IL-2, $CD8^+$